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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/561,034

Applicant(s)

CHRISTA ET AL.

Examiner

ZACHARY C. HOWARD

Art Unit

1646

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 November 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-49 is/are pending in the application.
- 4a) Of the above claim(s) 27-36, 40 and 44-49 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-26, 37-39 and 41-43 is/are rejected.
- 7) ☒ Claim(s) 19 is/are objected to.
- 8) ☒ Claim(s) 18-49 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 December 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 7/24/06
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 11/9/09 has been entered in full. Claim 36 is amended.
Claims 18-49 are pending.

Election/Restrictions

Applicants' election without traverse of Group I, claims 18-26 and 37-43, in the reply filed on 11/9/09 is acknowledged.

Claims 27-36 and 44-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed 11/9/09.

Applicants' election of hepatocyte as the species of cell in the reply filed on 11/9/09 is acknowledged.

Claim 40 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 18-26, 37-39 and 41-43 are under consideration, as they read upon the elected species.

Claim Objections

Claim 19 is objected to because of the following informalities:

Line 2 of claim 19 recites, "...as comprising an the amino acid sequence..." In this recitation, the word "an" is extraneous; the claim should simply recite "...as comprising the amino acid sequence..."

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites, "The pharmaceutical composition of claim 25, further defined as resulting in limited liver necrosis during use". The recitation of "resulting in limited liver necrosis during use" is indefinite because it appears to be a method step rather than a functional characteristic of the claimed composition.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-20, 23-26, 37-39 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(1) a pharmaceutical composition comprising a polypeptide comprising SEQ ID NO: 1 and a physiologically acceptable carrier, or a cell; and

(2) an isolated cell comprising an expression cassette that drives expression of a polypeptide comprising SEQ ID NO: 1, and a pharmaceutical composition comprising said cell,

does not reasonably provide enablement for

(3) a pharmaceutical composition comprising a polypeptide comprising an amino acid sequence having at least 90% amino acid identity with the amino acid sequence from amino acid residue 36 to amino acid residue 175 of SEQ ID NO: 1 and at least one physiologically acceptable carrier, or a cell; or

(4) a cell comprising an expression cassette that drives expression of a polypeptide comprising an amino acid sequence having at least 90% amino acid identity with the amino acid sequence from amino acid residue 36 to amino acid residue 175 of SEQ ID NO: 1, or a pharmaceutical composition comprising said cell.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a composition comprising a polypeptide related to SEQ ID NO: 1, which is the sequence of human HIP/PAP protein (hepatocarcinoma-intestine-pancreas/pancreatic-associated protein), and cells expressing said polypeptide. In some embodiments, the polypeptides must be effective to stimulate liver regeneration "*in vivo*" (claim 23) or "after chronic or acute liver failure" (claim 24). Claims 25 and 26 are directed to compositions that also include a "therapeutically effective amount of a hepatotoxic compound". The specification in ¶ 97 (published application) provides examples of therapeutic hepatotoxic compounds including "anaesthetics, such as Enflurane, neuropsychotropics such as Hydrazides, anticonvulsants such as valproic acid, analgesics, such as Acetaminophen, antimicrobials such as Amphotericin B or Penicillin, hormones such as Acetohexamides, cardiovascular drugs, such as Papaverine, Immunosuppressives and antineoplastics, such as asparaginase, anti-hypertension drugs, anti-inflammatory drugs and miscellaneous drugs such as vitamin A, Oxyphenisatin, Iodide Ion". The specification teaches that co-administration of said therapeutics with the polypeptide of the invention can protect against the hepatotoxic effects (¶ 89).

The specification provides the following working examples in support of the claimed invention. Example 1 is titled "Characterization of human HIP/PAP transgenic mice" and describes transgenic mice in which the human HIP/PAP transgene was specifically expressed in the liver. Example 2 is titled "Liver regeneration is stimulated in

mice expressing the human HIP/PAP gene" and teaches that "liver recovery was higher in the HIP/PAP transgenic than in wild-type mice" following partial hepatectomy (pg 37). Example 3 is titled "HIP/PAP mitogenic effect in primary culture hepatocytes" and teaches that hepatocytes derived from HIP/PAP transgenic mice have increased DNA synthesis as compared to wildtype hepatocytes, and that HIP/PAP protein added to wild type hepatocytes in primary culture increases DNA synthesis. Example 4 is titled "HIP/PAP anti-apoptotic effect against apoptosis induced by TNF- α + ActD in primary culture hepatocytes" and teaches that "hepatocytes expressing HIP/PAP resisted TNF- α + ActD – induced apoptosis after a 16-17 hours of treatment" and that cell survival was increase significantly over cells not expressing HIP/PAP. Example 5 is titled "Liver regeneration is stimulated in mice by administration of hepatocytes isolated from HIP/PAP transgenic mice" and teaches that in an *in vivo* mouse model of partial hepatectomy, hepatocytes isolated from human HIP/PAP-expressing transgenic mice persisted after transplantation and resulted in significantly higher liver mass 8 days after surgery as compared to mice not receiving said cells. Example 6 is titled "Liver regeneration is stimulated mice in by administration of HIP/PAP" and teaches a similar effect for injection of purified HIP/PAP in the same model used in Example 5. Example 7 is titled "Liver regeneration and mitose are stimulated in C57Bl6 mice by administration of HIP/PAP" and teaches that stimulatory effects of HIP/PAP on DNA synthesis and mitosis can be observed at 46 hours after surgery in the same model used in Example 5. Example 8 is titled "Expression of liver cytokines and activation of the STAT3 transcription factor during the time course of liver regeneration" and shows that the expression of STAT3 increases after surgery but returns to lower levels, and that TNF- α expression is inhibited 46 after surgery (the specification teaches that expression of each is needed for initiation of liver regeneration but that persistent expression will inhibit regeneration). Example 9 is titled "HIP/PAP is a protective drug against APAP-induced acute liver failure" and teaches a mouse model of human acute liver failure using acetaminophen, that HIP/PAP transgenic mice showed greater survival rate after 24 hours than wild type mice in such a model, and that HIP/PAP injection also increased the survival rate of wild type mice in such a model. Example 10 is titled

"HIP/PAP protein exhibits no toxic effects during the long-term *in vivo* follow-up of HIP/PAP expressing transgenic mice" and teaches that in two models of HIP/PAP transgenic mice with liver specific expression, "[n]one of the HIP/PAP-expressing mice had developed liver (or other) tumors, after a two-year follow-up period" (pg 44). Example 11 is titled "HIP/PAP delays HCC development in predisposed transgenic mice" and teaches an increase in survival of bi-transgenic mice (human HIP/PAP + WHV/c-myc) versus WHV/c-myc single transgenic mice (which causes liver cancer), Thus "HCC [hepatocellular carcinoma] onset is delayed in mice carrying both transgenes ... (Figure 13)" (pg 44). The results described in the working examples are supported by the results described in the publication of Simon et al (2003. FASEB J. 17: 1441-1450; reference C3 on the 7/24/06 IDS).

In view of the teachings of the specification and the relevant art showing the effectiveness of administration of HIP/PAP in stimulating liver regeneration in an *in vivo* model, and having a protective effect in an *in vivo* model of hepatotoxicity of a therapeutic (acetaminophen), the specification provides enablement for the pharmaceutical use of composition comprising a polypeptide comprising SEQ ID NO: 1 and a physiologically acceptable carrier, or a cell, including for the intended use of stimulating liver regeneration *in vivo*, and for isolated cells comprising an expression vector encoding a polypeptide comprising SEQ ID NO: 1. However, the specification fails to provide enablement for the following embodiments encompassed by the claims:

(1) The specification does not give any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO: 1 and variants of said protein. The broadest claims are directed to polypeptides comprising an amino acid sequence having at least 90% identity with residues 36-175 of SEQ ID NO: 1 (139 amino acids). Ten percent variation in 139 amino acids includes up to 13 amino acid changes. In addition, the broadest claims also permits residues 1-35 of SEQ ID NO: 1 to be changed. While residues 1-26 represent the signal sequence, residues 27-35 are part of the mature protein. Thus, claim 1

encompasses proteins with up to 22 amino acid differences from the mature HIP/PAP polypeptide (residues 27-175 of SEQ ID NO: 1; 148 amino acids).

To put the situation in perspective, the number of possible amino acid sequences that are 148 amino acids in length is 20^{148} . The number of possible amino acid sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \dots + X^{n-1}L(L-1)(L-2)\dots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\dots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence ($X = 19$ for a polypeptide sequence), L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For example, for a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23} . Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1×10^{26} . So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^n L^n / n!$, where $n \ll L$. Using this formula to approximate N in this example gives a value of 1.7×10^{26} .

Applying this to an example from the instant claims, the reference amino acid sequence of residues 36-175 of SEQ ID NO: 1 is 139 amino acids long. A sequence that is at least 90% identical to residues 36-175 of SEQ ID NO: 1 tolerates up to 13 amino acid changes. Therefore, the total number of possible amino acid sequences that are at least 90% identical to residues 36-175 of SEQ ID NO: 1 is about 5×10^{34} ($(19^{13} * 139^{13})/13!$). Thus, while limiting the scope of potential sequences to those that are at least 90% identical to a reference reduces the number of potential sequences to test (as

compared to having no structural limitation at all), it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which encode a protein with functional therapeutic activity. Such a genus is so vast that it would clearly require undue experimentation for the skilled artisan to make and test even a representative number of species from the genus. Furthermore, as described above the broadest claims also included mutation of any of residues 27-36 of the mature protein, further increasing the size of the vast genus of variants to be made and tested for functional therapeutic activity.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry 29(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, the specification provides little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a

starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(2) Claims 41-43 are directed to cells expressing a polypeptide of SEQ ID NO: 1. The specification contemplates three subgenera in which such host cells can be made and used. Specifically, the specification contemplates making and using the host cells in culture; in multicellular, transgenic organisms; and in gene therapy:

(i) The specification contemplates making and using isolated host cells in culture to produce the encoded protein recombinantly. Such is enabled, since the specification

and prior art provide specific guidance on how to make and use host cells for this purpose. Undue experimentation would not have been required of the skilled artisan to make and use the claimed host cells in this context.

(ii) The specification also asserts that the claimed gene products can be expressed in transgenic animals. However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the encoded peptide, other than transgenic mice expressing human HIP/PAP of SEQ ID NO: 1. The unpredictability of the art is *very high* with regards to making transgenic animals other than mice. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells that can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

(iii) The claims also encompass non-isolated host cells (found in an organism) comprising nucleotide constructs comprising the claimed gene produced by administering a nucleic acid (gene therapy). However, the specification does not teach any methods or working examples that indicate the claimed nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of

vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must be designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to generate a transgenic animal (other than a mouse) expressing the disclosed protein and to introduce and express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Please note that this rejection could be overcome by amending the claims to recite, for example, "An isolated host cell..." because such an amendment would clarify

that the claims are directed only to host cells that are to be made and used in culture as described in context (i) above.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 18-20, 23-26, 37-39 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 18-20, 23-26, 37-39 and 41-43 are genus claims because the claims are directed to compositions and cells comprising variant polypeptides. As described above, in the section titled, "Claim Rejections - 35 U.S.C. 112, 1st Paragraph, enablement" the genus of polypeptides encompassed by the claims is highly variant because a significant number of structural differences between genus members are permitted. The claims do not require that the polypeptides possess any particular conserved structure or function, or other disclosed distinguishing feature. The claims only require the claimed polypeptides share some structural similarity to the isolated polypeptide of SEQ ID NO: 1. Thus, the claims are drawn to a genus of polypeptides defined only by sequence similarity. However, the instant specification fails to describe the entire genus of polypeptides that are encompassed by each of these claims. From the specification, it is clear that Applicants has possession of an isolated polypeptide of SEQ ID NO: 1, and a polypeptide comprising residues 27-175 of SEQ ID NO: 1 (mature HIP/PAP protein), and thus compositions and cells comprising said polypeptides. The specification fails to describe or teach any other polypeptide which differs from the sequence of residues 27-175 of SEQ ID NO: 1 and that retains the characteristics of the parent polypeptide.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics

coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred,

regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only (1) a pharmaceutical composition comprising a polypeptide comprising SEQ ID NO: 1 and a physiologically acceptable carrier or cell; and (2) an isolated cell comprising an expression cassette that drives expression of a polypeptide comprising SEQ ID NO: 1 and a pharmaceutical composition comprising said cell, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-25, 37-39, 41 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Christa et al, 1996 (Am J Physiol. 271: G993-G1002).

The recitation of "pharmaceutical" in the preamble of claim 18 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re*

Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). Furthermore, a polypeptide comprising an amino acid sequence having at least 90% amino acid identity with the amino acid sequence from amino acid residue 36 to amino acid residue 175 of SEQ ID NO: 1 encompasses the mature 16 kDa human HIP/PAP polypeptide (residues 26-175 of SEQ ID NO: 1).

Thus, claim 18 encompasses a composition comprising a polypeptide that is residues 26-175 of SEQ ID NO: 1 and at least one physiologically acceptable excipient. The specification defines "physiologically acceptable excipient" as "solid or liquid filler, diluent or substance, which may be safely used in systemic or topical administration" (§ 103 of the published application). Christa et al teach transgenic mice overexpressing human HIP/PAP, which is a soluble secreted protein, and purification of said protein from the milk of said mice (pg G994). Milk from the mice is encompassed by the phrase "physiologically acceptable carrier" (as defined in the instant specification). Christa et al further characterize the protein as starting as having a molecular weight of 16 kDa (mature human HIP/PAP protein) as compared to 19 kDa (pre-HIP/PAP protein)(pg G996). Thus, Christa et al teach a composition comprising a protein that is residues 26-175 of SEQ ID NO: 1 (mature human HIP/PAP) and a physiologically acceptable carrier (milk). Therefore, the teachings of Christa et al anticipate claim 18.

Claim 19 depends from claim 18 and limit the polypeptide to one comprising the amino acid sequence from amino acid residue 36 to amino acid residue 175 of SEQ ID NO: 1. As described above, the mature 16 kDa human HIP/PAP protein (residues 27-175 of SEQ ID NO: 1) comprises residues 36-175 of SEQ ID NO: 1. Therefore, the teachings of Christa et al described above also anticipate claim 19.

Claims 20 and 21 each depend from claim 18 and encompass a composition comprising a polypeptide that comprises the amino acid sequence from amino acid residue 27 to amino acid residue 175 of SEQ ID NO: 1. Therefore, the teachings of Christa et al described above also anticipate claims 20 and 21.

Claim 22 depends from claim 18 and recites "wherein the polypeptide is further defined as a human hepatocarcinoma-intestine-pancreas/pancreatic-associated protein (HIP/PAP) with the amino acid sequence of SEQ ID NO: 1". This is interpreted as

limiting the polypeptide of claim 18 to one that is SEQ ID NO: 1. Christa et al further teach purified pre-HIP/PAP protein (expressed in recombinant *E. coli*) in 50 mM acetic acid buffer, pH 2.9 (pg G994). The instant specification teaches that a formulation comprising a physiologically acceptable have a pH that preferably "ranges anywhere from about 3 to about 8". A pH of 2.9 is interpreted as being encompassed by "about 3". Therefore, Christa et al also teach a composition comprising a protein that is residues 1-175 of SEQ ID NO: 1 (human pre-HIP/PAP protein) and a physiologically acceptable carrier (acetic acid buffer, pH 2.9).

Claims 23 and 24 each depend from claim 18 and limit the polypeptide to one "comprised in an amount effective to stimulate liver regeneration *in vivo*" (claim 23) or "comprised in an amount effective to stimulate liver regeneration after chronic or acute liver failure" (claim 24). The specification does not provide a limiting definition of an "effective amount" of HIP/PAP polypeptide in a composition, but provides the following exemplary amount: "for example, from on the order of about 6 µg/ml to about 10 mg/ml" (§ 104 of the published application). Christa et al further teach that "[p]roduction was estimated roughly at 100 µg HIP/PAP protein/ml milk" (pg G994). 100 µg/ml falls within the range of "about 6 µg/ml to about 10 mg/ml"; therefore, the teachings of Christa et al also anticipate claims 23 and 24.

Claim 25 depends from claim 18 and limits the composition to one further "comprising a therapeutically effective amount of a hepatotoxic compound". The specification (§ 87 of the published application) teaches that a hepatotoxic compounds include therapeutics including "antimicrobials such as Amphotericin B or Penicillin". The specification does not provide a limiting definition of "a therapeutically effective amount" of said compounds; therefore, this phrase is broadly interpreted as encompassing any amount of such antimicrobials (because any amount will kill microbes to some degree). As described above, Christa et al further teach expression of pre-HIP/PAP protein (SEQ ID NO: 1) in recombinant *E. coli*. Christa et al further teach said *E. coli* cells in Terrific Broth medium. Such is a composition comprising the polypeptide of SEQ ID NO: 1 (i.e., the composition comprises cells comprising the polypeptide of SEQ ID NO: 1). Christa et al further teach that the medium included ampicillin (200 µg/ml) and kanamycin (25

µg/ml). Ampicillin is part of the penicillin family of antibiotics and is thus encompassed by the antimicrobials taught by the specification. Therefore, Christa et al teach a composition comprising a polypeptide of SEQ ID NO: 1 and a therapeutically effective amount of a hepatotoxic compound (ampicillin). Thus, the teachings of Christa et al anticipate claim 25.

Claim 37-39 each encompass a composition comprising a polypeptide that is SEQ ID NO: 1 (human pre-HIP/PAP) and a cell that is a dividing hepatocyte. Christa et al teach that "[p]re-HIP/PAP ... form a support for the adhesion of rat hepatocytes in a dose-dependent manner" (pg G999). The hepatocytes were added in a "serum-free medium" and "with ... a 15-min preincubation with pre-HIP/PAP". Furthermore, the hepatocytes were freshly isolated from rats and thus were dividing hepatocytes. Thus, Christa et al teach a composition (serum-free medium) comprising a polypeptide that is SEQ ID NO: 1 (human pre-HIP/PAP) and dividing hepatocytes (isolated from rats). Therefore, the teachings of Christa et al also anticipate claims 37-39.

Claim 41 encompasses a cell comprising an expression cassette that drives expression of a polypeptide that is residues 1-175 of SEQ ID NO: 1. Christa et al further teach that "HIP/PAP protein was expressed in *E. coli* by cloning HIP/PAP cDNA in the plasmid Quiagen [sic] expression vector (pQE)" and "we chose to express the whole coding HIP/PAP cDNA" (pg G994). Said *E. coli* cells are cell comprising an expression cassette that drives expression of a polypeptide that is residues 1-175 of SEQ ID NO: 1 (mature human HIP/PAP). Thus, the teachings of Christa et al anticipate claim 41.

Claim 43 encompasses a pharmaceutical composition comprising either (1) polypeptide that is residues 1-175 of SEQ ID NO: 1 and a cell, or (2) a cell comprising an expression cassette that drives expression of a polypeptide that is residues 1-175 of SEQ ID NO: 1. The recitation of "pharmaceutical" in the preamble of claim 43 is interpreted as an intended use and bears no accorded patentable weight to distinguish a claimed product over one from the prior art, for the same reasons as described above for claim 18. Christa et al further teach said *E. coli* cells in Terrific Broth medium. Such is a composition comprising said *E. coli* cells and a polypeptide (pre-HIP/PAP, expressed by said cells and found within said cells) and thus anticipates embodiment

(1) of claim 43. Furthermore, such is a composition comprising a cell comprising a recombinant vector driving expression of a polypeptide of SEQ ID NO: 1 and thus anticipates embodiment (2) of claim 43.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Christa et al (1996. Am J Physiol. 271: G993-G1002), as applied to claim 41 above, and further in view of Tanaka et al (1997. Hepatology. 26(3): 598-604).

The teachings of Christa et al that anticipate claim 41 are described above. While Christa et al teach recombinant expression of HIP/PAP in *E. coli* cells, Christa et al do not teach recombinant expression of HIP/PAP in a hepatocyte.

Christa et al further teach that HIP/PAP is expressed in hepatocarcinoma (see Abstract) but not in normal liver cells (pg G999).

Tanaka et al teach liver-specific overexpression of the gene hIRS-1 (human insulin receptor substrate-1) in hepatocytes from transgenic mice, and that "overexpression of hIRS-1 in the transgenic liver led to increased hepatocyte DNA synthesis" and thus "may potentially enhance tumor progression" (see Abstract).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to replace HIP/PAP as taught by Christa et al for hIRS-1 in the transgenic mice taught by Tanaka et al. The person of ordinary skill in the art would have been motivated to do so in order to determine if overexpression of HIP/PAP would cause increased hepatocyte DNA synthesis (i.e., to determine if the link between HIP/PAP expression in hepatocarcinoma is due to overexpression of HIP/PAP). A person of ordinary skill in the art would have had a reasonable expectation of success in creating the transgenic mice with liver-specific gene expression of HIP/PAP because Tanaka et al teach a method of producing a transgenic mice with liver-specific gene expression that can be applied to any gene of interest, and Christa provide a recombinant HIP/PAP gene sequence that can be used as a gene of interest.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Application/Control Number: 10/561,034

Page 20

Art Unit: 1646

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Primary Examiner, Art Unit 1647